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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,737	06/04/2001	Haifan Lin	180/104/2	6886

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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/873,737	Lin
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Dec 2, 2002 .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-98 is/are pending in the application.

4a) Of the above, claim(s) 1-13, 30-48, and 50-98 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 14-17, 20-29, and 49 is/are rejected.

7) ☒ Claim(s) 18 and 19 is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on Jun 4, 2001 is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election of Group II claims, *e.g.,* claims 14-29, and 49, and more specifically the group of claims directed to SEQ ID NO: 5 in the response filed December, 2002 is acknowledged. Because applicant did not distinctly and specifically point out the supposed error in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-13, 30-48, 50-98, drawn to non-elected claimed inventions have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Elected claims 14-29, and 49, drawn to the subject matter relevant to SEQ ID NO: 5, to which the following grounds of rejection are applicable, are pending.

Elected claim 49, and claims 14 and claims dependent there from are objected because the claims are dependent on non-elected claims, and/or attempt to refer to non-elected claims. The claims should be amended so as to only reflect the elected claimed invention and/or to refer to only presently pending elected claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Elected claims 14-17, 20-29, and 49, embracing claimed subject matter of variants and/or a genus of vertebrate and/or invertebrate nucleic acid sequences which are not necessarily related in any way to the disclosed structures of the cloned and purified *Drosophilae,* murine, and human *piwi* genes, and at best are only required to be similar in functions as a protein that enhances growth, proliferation, and/or self-renewing division of stem cell, which nucleic acid

sequences embraces potential genes similar to that of the disclosed *piwi* genes are yet to be discovered , are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Below are a summary of the claimed invention and/or applicant's breadth of the claims on the basis of the as-filed specification:

1/ Breadth of the claimed subject mater:

[0003] The present invention relates generally to isolated and purified proteins and nucleic acids which modulate stem cell renewal, growth and division and which modulate primordial germ cell proliferation. More particularly, the present invention relates to isolated and purified piwi family proteins and isolated and purified polynucleic acids encoding the same.

[0014] The present invention also provides an isolated and purified polynucleotide that encodes a polypeptide that plays a role in the growth, proliferation and self-renewing division of stem cells, and proliferation of primordial germ cells. In a preferred embodiment, a polynucleotide of the present invention comprises a DNA molecule from a vertebrate species. Preferred vertebrates comprise mammals, birds orfish. A preferred mammal is a human. More preferably, a polynucleotide of the present invention encodes a polypeptide designated PIWI. Even more preferably, a polynucleotide of the present invention encodes a polypeptide comprising an amino acid residue sequence of any of SEQ ID NOs:2, 4 and 6. Most preferably, an isolated and purified polynucleotide of the invention comprises a nucleotide base sequence of any of SEQ ID NOs:1, 3 and 5.

[0053] As used in the following detailed description and in the claims, the term "piwi family" refers to a family or group of genes and gene products including, but not limited to, PIWI, HIWI, MIWI, PRG-1 and PRG-2 proteins, and the piwi, hiwi, miwi, prg-1 and prg-2 genes, each of which are further defined herein. The term "piwi family" also includes other members of the piwi family of genes and gene products characterized by biological activity, including but not limited to the biological activities of modulating growth, proliferation and/or self-renewing division of stem cells, and/or proliferation of primordial germ cells.

[0054] Preferably, piwi family genes and gene products are isolated from eukaryotic sources. Thus, the term "piwi family" also includes invertebrate homologs. The term "piwi family" further includes vertebrate homologs of piwi family members, including, but not limited to, mammalian, avian and fish homologs. Preferred mammalian homologs of piwi family members include, but are not limited to, murine and human homologs.

[0061] In certain embodiments, the invention concerns the use of piwi family genes and gene products that include within their respective sequences a sequence which is essentially that of a piwi family gene, or the corresponding protein. The term "a sequence essentially as that of a piwi family gene", means that the sequence substantially corresponds to a portion of a piwi family polypeptide or piwi family gene and has relatively few bases or amino acids (whether DNA or protein) which are not identical to those of a piwi family protein or piwi family gene, (or a biologically functional equivalent of, when referring to proteins). The term "biologically functional equivalent" is well understood in the art and is further defined in detail herein. Accordingly, sequences which have between about 70% and about 80%; or more preferably, between about 81% and about 90%; or even more preferably, between about 91% and about 99%; of amino acids which are identical or functionally equivalent to the amino acids of a piwi family protein or piwi family gene, will be sequences which are "essentially the same".

Biologically Functional Equivalents

[0088] As mentioned above, modification and changes may be made in the structure of the piwi family proteins and peptides described herein and still obtain a molecule having like or otherwise desirable characteristics. For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive capacity with structures such as, for example, in the nucleus of a cell. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence (or, of course, its underlying DNA coding sequence) and nevertheless obtain a protein with like or even countervailing properties (e.g., antagonistic v. agonistic). It is thus contemplated by the inventor that various changes may be made in the sequence of the piwi family proteins and peptides (or underlying DNA) without appreciable loss of their biological utility or activity.

2/ Description of guidance and/or working example on the basis of the as-filed specification:

[0260] The purification and isolation of cDNAs representing piwi family genes from human, mouse, and Drosophila are disclosed in the Examples, along with the primary sequence of the PIWI proteins in human, mouse and Drosophila as deduced from the isolated cDNA sequences.

[0261] Further, the identification of piwi homologous genes, prg-1 and prg-2, and their role in germline self-renewal in *C. elegans* is described in the Examples. The identification of two piwi family-like genes in Arabidopsis, Zwille and argonaute(ago), that are required for meristem cell divisions is also described.

[0262] A highly conserved protein signature motif of 43-amino acid residues, the PIWI box, that exists in piwi family genes from human, mouse, Drosophila, *C. elegans*, and Arabidopsis, as well as in a broader class of novel genes is also described in the Examples.

[0263] The demonstration that the PIWI and MIWI proteins are nuclear proteins is also disclosed.

[0264] The essential function of piwi for Drosophila germline stem cell growth, proliferation and self-renewal and also for early embryonic development is also disclosed.

[0265] The specific expression pattern of miwi and hiwi in the adult murine and human testis, respectively, but not in the adult murine or human ovary which do not contain germline stem cells is also demonstrated in the Examples. miwi is further shown to be expressed in germline stem cells (and specifically not in somatic cells) of the mouse testis.

[0266] The essential role of piwi family genes in mammalian spermatogenesis is also disclosed. A null mutation of miwi, wherein most of the miwi sequence is deleted, results in male infertility with specific defects during early stages of spermatogenesis. A mutation that specifically deletes miwi sequences encoding the PIWI box show abnormalities indistinguishable from those of the null mutant, demonstrating the essentiality of the **PIWI** box for piwi gene functions.

[0267] Also disclosed is a demonstration that miwi contributes to the long term self-renewing ability of hematopoietic stem cells.

[0268] Thus, as disclosed herein, the function of piwi family genes in regulating proliferation of germ cells and other stem cells is conserved among human, mouse, Drosophila, *C. elegans*, and Arabidopsis.

[0270] piwi encodes a highly basic novel protein well conserved during evolution. This Example also describes the isolation of piwi family homologs in *C. elegans* and human. This Example further describes the identification of Arabidopsis piwi family-like genes known to be required for meristem cell maintenance. Decreasing *C. elegans* piwi expression reduces the proliferation of GSC-equivalent cells. Thus, piwi represents a novel class of genes required for GSC division in diverse organisms.

[0300] To determine whether the PIWI protein is conserved during evolution, applicant searched for its homologous sequences at the protein level and identified two ORFs of unknown function from *C. elegans* and an expressed sequence tag (EST, AA43031.1) from a human testis CDNA library. Applicant isolated and sequenced cDNAs for the two *C. elegans* genes, herein named prg-1 and prg-2 (prg for piwi-related gene) to verify their homology to *Drosophila piwi*. The prg-1 and prg-2 genes share 40.1% and 38.5% amino acid identity to piwi, respectively, over their entire length. In the C-terminal 104 amino acid region, the homology increases to 55.8% and 56.7%, respectively. Moreover, prg-1 and prg- 2 are 90% identical to each other over their full length and 98% identical at the C-terminus. This high degree of homology suggests that prg-1 and prg-2 may represent a gene duplication event. The two clones differ primarily in that prg-1 is 60 amino acids longer at the N-terminus than prg-2. Using ACeDB (Thierry-Mieg and Durbin, 1992), prg-1 was mapped to chromosome I between unc-15 and gld-1 in cosmid D2030 and prg-2 was mapped to chromosome IV, between unc-44 and smg-7 on cosmid CO1G5.

[0301] To isolate human piwi homologs, the human EST (0.9 kb) clone was sequenced and used to screen a human testis cDNA library. A resulting 2.3 kb partial cDNA, herein named hiwi (for human pwi), shows 47.1% identical amino acid sequence to the *Drosophila piwi* over its full length, with 58.7% identity at the C-terminus. No piwi-related sequences were found from bacteria or yeast genomes whose entire sequences are known. This is consistent with the stem cell-related function of piwi and indicative of piwi family-like genes specific for multicellular organisms.

[0342] Protein sequence analysis showed that HIWI is 36.6% identical to *Drosophila PIWI* at amino acid level over its full length and 58.7% identical at the C terminal 104 amino acid residues. HIWI also shares 33.4% and 33.1% identity with two *C. elegans* PIWI family homologs PRG-1 and PRG-2 over its full length while the percentage increased to 57.7% and 58.7% at the C-terminals, suggesting piwi family genes and gene products are conserved during evolution. In addition, the higher degree of sequence homology between the C terminals suggests a conserved role of the C-terminal domain of PIWI in protein function.

[0303] PIWI, PRG-1, PRG-2, and HIWI differ from ZLL and AGO proteins, and especially from the 13 additional putative *C. elegans* proteins, predominantly at the N-terminus, suggesting that this region may be involved in piwi-specific function. The C-terminal conservation suggests that this region of PIWI may contain a novel functional domain that plays an important role for the general activity of these proteins in diverse biochemical processes, with the N-terminus rendering the specificity of the activity.

[0304] To examine the C-terminal region of homology more closely, the sequences were aligned using Block Maker™, which reveals characteristic regions of protein families (Henikoff et al., 1995) **(FIG. 2)**. Block Maker™ analysis identified a 43 amino acid domain conserved among all 22 proteins, within which five residues are absolutely conserved with defined spacing. Eight more residues are also conserved with defined spacing among all known genes across the phyla except for several *C. elegans* ORFs with unknown function. This region is referred to herein as the PIWI box and represents a novel conserved functional motif. PIWI, that is the piwi family of gene products, thus represents a novel class of evolutionarily conserved proteins with conserved functionality, as described herein below.

[0358] The miwi ORF predicts that the MIWI protein contains 862 amino acid residues (**FIG. 6**), with a relative molecular mass (M) of 98,600 and an isoelectric point of 9.46. Except for a 100-200 amino acid stretch at the N-terminus, MIWI shares significant homology over its entire length with other PIWI family proteins, such as MILI from mice (GenBank GI No. 7416113; 42% identity), HIWI (Cox et al., 1998; 94% identity) and HILI (GenBank GI No. 8922370; 46% identity) from humans, PIWI (Cox et al., 1998; 37% identity) and AUBERGINE (Wilson et al., 1996; Schmidt et al., 1999; 38% identity) from Drosophila, PRG-1 and PRG-2 from *C. elegans* (Cox et al., 1998; 34% and 33% identity), and PAP from Paramecium (GenBank GI No. 6630673; 28% identity, respectively). Interestingly, all these proteins are either involved in the development of the germline or its equivalent. The homology at the C-terminal PIWI Box region is particularly high (**FIG. 6**), suggesting the potential importance of this region for the MIWI protein function.

[0359] miwi is specifically expressed in the germline during spermatogenesis.

Thus, it is apparent that on the basis of the as-filed specification, the as-filed specification only provide sufficient description of the claimed subject matter drawn to an isolated and purified polynucleic acid encoding a biologically active *piwi* family polypeptide, wherein the polynucleic acid is at least about 75% identical to a DNA sequence as set forth in any of SEQ ID NOS: 1, 3 and 5, and wherein the polypeptide comprises the PIWI box.

The claims are readable on a genus of *piwi* genes, allelic variants, which not only embrace *piwi* family genes (as defined loosely by the as-filed specification) isolated from any and/or all vertebrate, fish, invertebrate or avian species, but also embrace any gene which does not necessarily required to have common structure to that of the disclosed Drosophilae, mouse, and human *piwi* cDNA. The as-filed specification and the claims basically contemplate that any isolated gene and/or cDNA, which is yet to be discovered but may be discovered later in any form, as long as the yet to be discovered gene and/or cDNA exhibit a biological function of modulating growth, proliferation, or self-renewing division of stem cells, and/or proliferation of primordial germ cells, would fall with the breadth of the claimed subject matter. An adequate written description of a polypeptide or protein or peptide requires more than a mere statement that it is part of the invention and reference to a potential method and/or assays for isolating it;

what is required is a description of the core structure of the claimed protein or polypeptide sequences itself. In essence, the core structure of a generic isolated *piwi* protein that a person skill in the art would have recognized that applicant was in possession at the invention was made is a genus of isolated and purified polynucleic acid encoding a biologically active *piwi* family polypeptide, wherein the polynucleic acid has at least about 75% or greater homology to a DNA sequence as set forth in any of SEQ ID NOS: 1, 3 and 5, and wherein the polypeptide comprises the PIWI box. Note that SEQ ID NOS 1, 3, and 5 all encode and/or contain the PIWI box coded DNA region which is deemed essential for its respective biological function, particularly on the basis of the as-filed specification. It is not sufficient to define protein sequences solely by its generic principal biological property, i.e. encodes a biologically active *piwi* family polypeptide wherein the term is defined loosely and broadly by the specification, encodes a biologically functional equivalent of any peptide fragment, regardless of its length, of SEQ ID NOS: 2, 4 and 6, being immunologically cross-reactive with antibodies with are immunologically reactive with peptides encoded by SEQ ID NOS 2, 4, or 6, or encodes unspecified DNA sequences as essentially, wherein the essentially is again defied loosely by the as-filed specification as being any sequence which is not necessarily identical in any portion of the sequence but rather only is required to have at least 70% of the amino acid resides being functionally equivalent to the amino acids of SEQ ID NO: 2, 4 or 6. The reason for the insufficiency of the as-filed specification to satisfy the written description requirement for such broad claimed subject matter is that other than the disclosure of no more than PIWI box containing *piwi* family polypeptide encoded polynucleic acids having at least about 75% or greater homology to a DNA sequence as set forth in any of SEQ ID NOS: 1, 3 and 5, the as-filed specification simply wishes to know the identity of any other *piwi* family gene and/or cDNA with a functionally equivalent activity , and yet is not necessarily a PIWI box containing *piwi* family polypeptide encoded polynucleic acid which has at least about 75% or greater homology to a DNA sequence as set forth in any of SEQ ID NOS: 1, 3 and 5. The claims as written clearly embrace a genus of *piwi* family polypeptide encoded polynucleic acids which have nothing to do with SEQ ID NOS: 2, 4, or 6, or any PIWI box containing protein derived from SEQ ID NOS: 2, 4, or 6. Thus, the as-filed specification does not reasonably provide

sufficient description of a representative number of *piwi* family polypeptide encoded polynucleic acids comprising a primary structure of particular amino acid residues, which are embraced by the breadth of the claimed invention. Claiming a genus of unspecified *piwi* family polypeptide encoded polynucleic acids that are yet to be discovered, wherein the essential feature of the particular sequences of *piwi* family polypeptide encoded polynucleic acids that would bring life and meaning to its claimed biological activity which achieves a result without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Note that a reasonable recognition by a skilled artisan on the basis of applicant's disclosure that applicant was in possession of one single subgroup of PIWI box containing *piwi* family polypeptide encoded polynucleic acids having at least about 75% or greater homology to a DNA sequence as set forth in any of SEQ ID NOS: 1, 3 and 5 is not sufficient to satisfy the written description for the broad subject matter being sought in the presently pending claims.

Elected claims 14-17, 20-29, and 49, embracing claimed subject matter of variants and/or a genus of vertebrate and/or invertebrate nucleic acid sequences which are not necessarily related in any way to the disclosed structures of the cloned and purified *Drosophilae,* murine, and human *piwi* genes, and at best are only required to be similar in functions as a protein that enhances growth, proliferation, and/or self-renewing division of stem cell, which nucleic acid sequences embraces potential genes similar to that of the disclosed *piwi* genes are yet to be discovered, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for claims limited to

1/ An isolated and purified polynucleic acid encoding a biologically active *piwi* family polypeptide, wherein the polynucleic acid is at least about 75% identical to a DNA sequence as set forth in any of SEQ ID NOS: 1, 3 and 5, and wherein the polypeptide comprises the PIWI box.

2/ A recombinant vector comprising the polynucleic acid of 1;

3/ An cultured cell comprising the recombinant vector of 2/.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

With respect the breadth of elected claims as set forth above, the claimed invention is not supported by a sufficient written description for possessing of the genus of proteins or polypeptides encoded polynucleic acid as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not known how to make and use the claimed invention so that it would operate as intended. Note that the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

Furthermore, Further, the problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. For example, while it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. As such, these or other regions in addition to the PIWI box or the C-terminal of SEQ ID NOS 2, 4 or 6, may also be critical determinants of the biological activity of the entire protein of SEQ ID NOS 2, 4, or 6. These regions can tolerate only relatively conservative substitutions or no substitutions (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction,

1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). However, Applicant has provided little or no guidance beyond the given scope of the enablement and/or written description requirement. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Brenner, 1999, Trends in Genetics 15: I32; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation unnecessary to determine an activity or property of the disclosed polypeptide such that it can be determined how to use any of the claimed protein, orthologs, variants, or fragment thereof to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity and the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular common and/or essential structure of those claimed as *piwi* family polypeptide encoded polynucleic acid, and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 49, readable on any recombinant cell or cell line suitable for use in expressing any *piwi* family polypeptide, wherein the cell does not necessarily comprise the polypeptide, is rejected under 35 USC 102(b) as being anticipated by Hogan (US Pat No. 5,690,926).

Hogan teaches an isolated embryonic cell or cell line containing isolated pluripotent embryonic cells (entire disclosure). Absent evidence to the contrary, the cells or cell line of Hogan is suitable for use in expressing any *piwi* family polypeptide.

Claims 18 and 19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

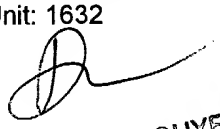
Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632



DAVE T. NGUYEN
PRIMARY EXAMINER